CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022047Orig1s000

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22047/000
Org Code : 130
Priority :

Sponsor: ASTRAZENECA (UK)
8355
WILMINGTON, DE 198038355

Stamp Date : 17-JUL-2006
PDUFA Date : 17-MAY-2007
Action Goal :
District Goal: 18-MAR-2007

Brand Name : SEROQUEL SR
Estab. Name:
Generic Name: QUETIAPINE FUMARATE
Dosage Form: (EXTENDED-RELEASE TAB
,ET)
Strength : 50, 200, 300, 400 MG

FDA Contacts: K. KIEDROW Project Manager 301
796-1924
P. SHIROMANI Review Chemist 301
796-2133
T. OLIVER Team Leader 301
796-1728

Overall Recommendation: ACCEPTABLE on 03-APR-2007by J. D AMBROGIO(HFD-
22) 301-827-

9073

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

(b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-AUG-06

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 9610616 FEI : 1000290327

ASTRAZENECA GMBH

OTTO-HAHN-STRASSE

PLANKSTADT, , GM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-APR-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2517100 FEI : 2517100

ASTRAZENECA PHARMACEUTICALS LP

587 OLD BALTIMORE PIKE

NEWARK, DE 197021307

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-DEC-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2518137 FEI : 2518137

ASTRAZENECA PHARMACEUTICALS LP

1800 CONCORD PIKE

WILMINGTON, DE 19850

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-DEC-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610422 FEI : 3002850317

ASTRAZENECA UK LTD

BUSINESS PK CHARTER WAY, SK102NA

MACCLESFIELD, CHESHIRE, UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-NOV-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-AUG-06

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

NDA 22-047
Amendment

Quetiapine fumarate
SEROQUEL® SR
50, 200, 300, & 400 mg Tablets

AstraZeneca

Prafull Shiromani, Ph.D.
and Wendy Wilson, Ph.D. (Artificial Neural Network)

Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-047

2. REVIEW #: 2

3. REVIEW DATE: 09-MAY-2007

4. REVIEWER: Prafull Shiromani, Ph.D.
Wendy Wilson, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
CMC Review 1	25-APR-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment: Sponsor's Responses to Agency's CMC Review Questions (IR3)	27-APR-2007
Updated Labeling Amendment	07-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca UK Limited
Address:	Alderley Park, Macclesfield, Cheshire, SK 10 4TG, England
Representative:	AstraZeneca Pharmaceuticals LP (Dr. Gary P. Horowitz), Wilmington, DE 19803-8355

Telephone: (302) 855-1008

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SEROQUEL® XR
b) Non-Proprietary Name (USAN): quetiapine fumarate
c) Code Name/# (ONDC only): ICI 204,636, ZD5077; ZM 204,636
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of schizophrnia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 50, 200, 300, & 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

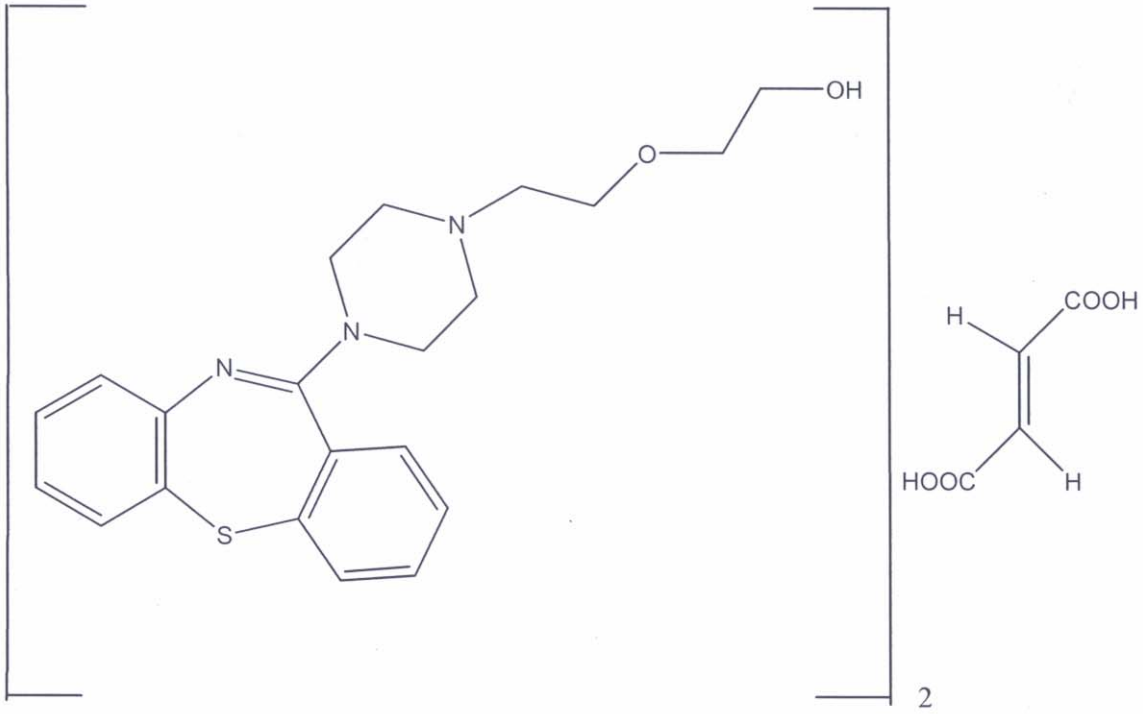
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-[2-(4-(Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperaziny-1)ethoxy]ethanol fumarate (2:1) (salt)

Molecular formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$
MW: 883.11
CAS: 111974-72-2



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Acceptable	03-APR-2007	J. D. Ambrogio
Pharm/Tox	N/A	N/A	None
Biopharm	Dissolution Acceptable as per Verbal Communication.		Kofi Kumi
DMETS	'SR' modifier not recommended	04-AUG-2006	Nora Roselle
Methods Validation	Samples not sent to Lab. since conventional methods	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable	09-NOV-2006	Ruth Ganunis
Microbiology	N/A	N/A	None

The Chemistry Review for NDA 22-047

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for **Approval** from a CMC perspective.
The applicant has provided adequate responses to several information request letters and to all the deficiencies delineated in CMC Review 1.

The overall evaluation from the Office of Compliance for cGMP compliance is **ACCEPTABLE.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

SEROQUEL XR tablets will be supplied as biconvex, film coated, capsule-shaped tablets containing 50, 200, 300 or 400 mg quetiapine fumarate (expressed as free base) packed in both HDPE bottles, with child resistant closures, and clear (b) (4) blister packs. The 4 strengths are differentiated by size, color (50 mg-peach colored tablets, 200 mg-yellow, 300 mg-pale yellow, and 400 mg-white), and intagliation. The drug substance is present in the tablets as the fumarate salt and all doses and tablet strengths are expressed as milligrams of base, not as fumarate salt.

SEROQUEL IR has been previously formulated as immediate release orally administered 25, 50, 100, 150, 200, 300 and 400mg tablets. These may be dosed either 2 or 3 times daily. A sustained release formulation has been developed to provide a once daily dosing regimen, so as to improve patient compliance and be beneficial clinically. The solubility, absorption and pharmacokinetic characteristics of quetiapine (BCS Class 2 category – low solubility and high permeability) are compatible with this development of a conventional sustained release tablet.

SEROQUEL SR (b) (4) are formulated using (b) (4) to obtain the sustained release (b) (4) of quetiapine.

To ensure formulation similarity across the product range the concentration of (b) (4)

An Artificial Neural Network (ANN) model has been developed, established and validated to reliably predict the optimal ratio, based on the (b) (4)

SEROQUEL SR 50, 200, 300 and 400 mg tablets, have been studied for stability under ICH conditions. The stability batches had the following ratios of (b) (4) . Since there was lack of stability information with product manufactured using other extremes (b) (4) in the original submission, the sponsor has now, at the request of FDA, provided stability data at ambient conditions on one additional 50 mg tablets formulated with this (b) (4) ratio and initiated a stability study on another batch. The observed stability data is consistent with that observed in previous stability evaluations thus, substantiating that the stability is independent of this ratio.
Stability studies, submitted in the original NDA, for the 200 mg and 300 mg tablets support a shelf life of 36 months in all commercial packages when stored at 25°C.
The applicant has augmented the twelve months stability data for the 50 mg and 400 mg tablets in the original submission with additional twelve months of satisfactory data. This data now supports a shelf life of 36 months (ref. ICH Q1E) for these strengths in all commercial packages when stored at 25°C.

Based on the Agency's concern the applicant now agrees to conduct degradation product testing at initial product release, where formerly this test was omitted from the product specification.

In response to an Agency concern the applicant asserts that any changes to the magnesium stearate level will be processed in accordance with the SUPAC MR guidance.

A recent Biopharm Review concludes that the sponsor's dissolution methodology and the IVIVC A are acceptable.

Drug Substance
The drug substance for the sustained release formulation remains unchanged compared to that (quetiapine fumurate) approved for NDA 20-639 for SEROQUEL immediate release tablets.

B. Description of How the Drug Product is Intended to be Used

SEROQUEL SR is a psychotropic agent indicated for the treatment of schizophrenia. It is to be administered once daily, preferably in the evening. The effective dose range is 400-800 mg per day depending on the response and tolerance of the individual patient. Patients who are currently being treated with divided doses of SEROQUEL (immediate release formulation) may be switched to SEROQUEL SR at the equivalent daily dose taken once daily. Individual dose adjustments may be necessary. The tablets should be swallowed whole and not split, or chewed or crushed.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-047) is recommended for **APPROVAL.**
There are no outstanding issues with regard to chemistry, manufacturing, and control.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani Ph.D, Wendy Wilson, Ph.D.
ChemistryTeamLeaderName/Date Ramesh Sood, Ph.D.
ProjectManagerName/Date Kimberly Updegraff

C. CC Block

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/s/

Prafull Shiromani
5/9/2007 11:30:08 AM
CHEMIST

Wendy I. Wilson
5/9/2007 11:32:55 AM
CHEMIST

Ramesh Sood
5/9/2007 03:25:37 PM
CHEMIST

NDA 22-047

Quetiapine fumarate
SEROQUEL® SR
50, 200, 300, & 400 mg Tablets

AstraZeneca

Prafull Shiromani, Ph.D.
and Wendy Wilson, Ph.D. (Artificial Neural Network)

Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-047

2. REVIEW #: 1

3. REVIEW DATE: 16-APR-2007

4. REVIEWER: Prafull Shiromani, Ph.D.
Wendy Wilson, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-047	17-JUL-2006
Quality Overall Summary	30-AUG-2006
Responses to Questions from FDA	25-JAN-2007
Response to Question from FDA	29-JAN-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca UK Limited
Address:	Alderley Park, Macclesfield, Cheshire, SK 10 4TG, England
Representative:	AstraZeneca Pharmaceuticals LP (Dr. Gary P. Horowitz), Wilmington, DE 19803-8355

Telephone: (302) 855-1008

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: SEROQUEL® SR
b) Non-Proprietary Name (USAN): quetiapine fumarate
c) Code Name/# (ONDC only): ICI 204,636, ZD5077; ZM 204,636
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Treatment of schizophrnia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 50, 200, 300, & 400 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

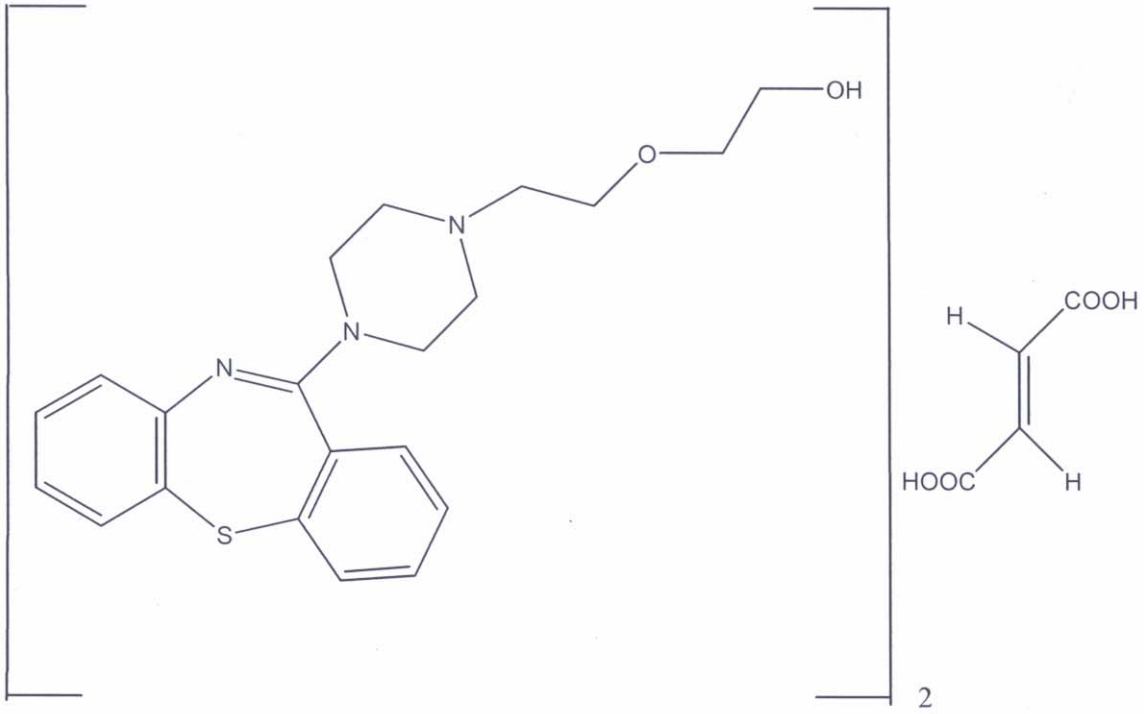
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-[2-(4-(Dibenzo[b,f][1,4]thiazepin-11-yl-1-piperaziny-1)ethoxy]ethanol fumarate (2:1) (salt)

Molecular formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$
MW: 883.11
CAS: 111974-72-2



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
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3 – Reviewed previously and no revision since last review
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	Acceptable	03-APR-2007	J. D. Ambrogio
Pharm/Tox	N/A	N/A	None
Biopharm	pending		
DMETS	'SR' modifier not recommended	04-AUG-2006	Nora Roselle
Methods Validation	Samples not sent to Lab. since conventional methods	N/A	None
OPDRA	N/A	N/A	None
EA	Acceptable	09-NOV-2006	Ruth Ganunis
Microbiology	N/A	N/A	None

The Chemistry Review for NDA 22-047

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended as "Approvable" from a CMC perspective.
The approvability of this application, from a CMC perspective, depends on the applicant's responses to the FDA IR letter sent to the applicant on 30-MAR-2007.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

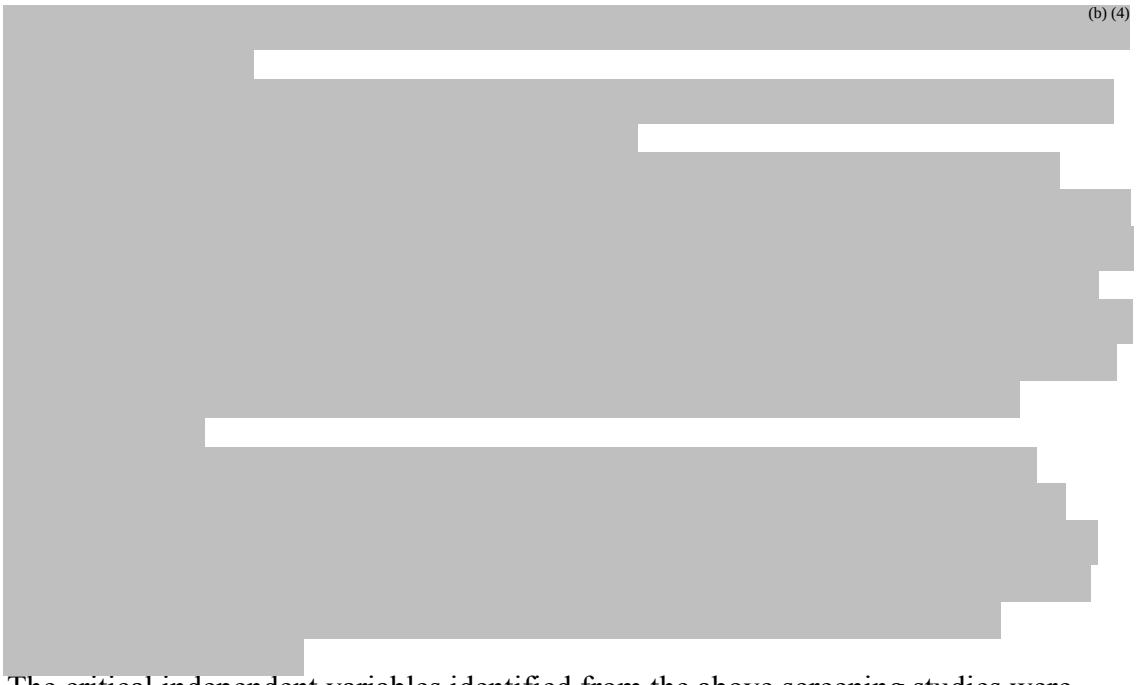
Drug Product

SERTOQUEL SR tablets will be supplied as biconvex, film coated, capsule-shaped tablets containing 50, 200, 300 or 400 mg quetiapine fumarate (expressed as free base) packed in both HDPE bottles, with child resistant closures, and clear (b) (4) blister packs. The 4 strengths are differentiated by size, color (50 mg-peach colored tablets, 200 mg-yellow, 300 mg-pale yellow, and 400 mg-white), and intagliation. The drug substance is present in the tablets as the fumarate salt and all doses and tablet strengths are expressed as milligrams of base, not as fumarate salt.

SEROQUEL IR has been previously formulated as immediate release orally administered 25, 50, 100, 150, 200, 300 and 400mg tablets. These may be dosed either 2 or 3 times daily. A sustained release formulation has been developed to provide a once daily dosing regimen, so as to improve patient compliance and be beneficial clinically. The solubility, absorption and pharmacokinetic characteristics of quetiapine (BCS Class 2 category – low solubility and high permeability) are compatible with this development of a conventional sustained release tablet.

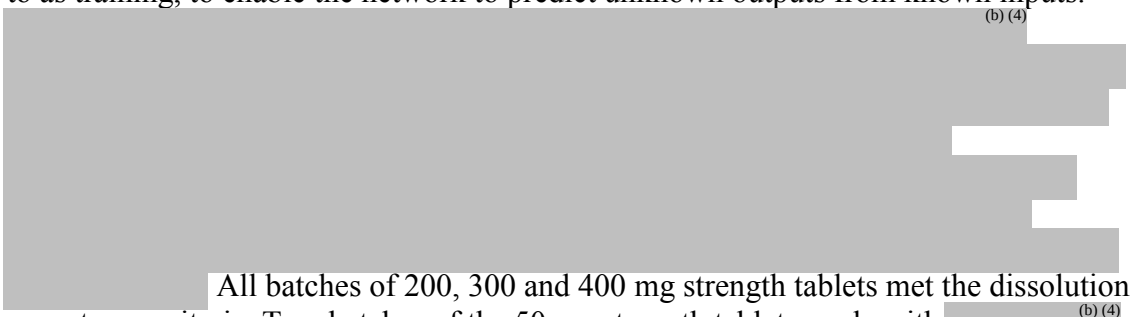
SEROQUEL SR (b) (4) are formulated using (b) (4) to obtain the sustained release (b) (4) of quetiapine. To ensure formulation similarity across the product range the concentration of (b) (4)

(b) (4)



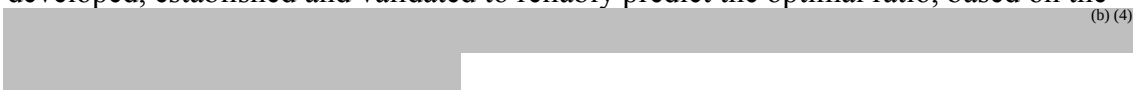
The critical independent variables identified from the above screening studies were used as input variables for the Artificial Neural Network (ANN) model. ANN was used to develop a correlation between known inputs and known outputs in a process referred to as training, to enable the network to predict unknown outputs from known inputs.

(b) (4)



All batches of 200, 300 and 400 mg strength tablets met the dissolution acceptance criteria. Two batches of the 50 mg strength tablets made with (b) (4) contents did not meet the acceptance criteria and this was explained as being due to the model being under-represented in terms of lots with (b) (4) contents in this region. The model will be updated with new data from commercial scale manufactures to improve model predictability. Thus, the ANN model has been developed, established and validated to reliably predict the optimal ratio, based on the

(b) (4)



A dissolution method has been developed using the pharmcopeial basket method with a rotation speed of 200 rpm, at pH of 4.8 for 5 hours, adjusted to pH 6.6 for the period of 5 to 20 hours. This method provides the best match to the in vivo release. The following dissolution acceptance criteria have been established: NMT (b) (4) at 1 hour, (b) (4) at 6 hours, (b) (4) at 12 hours and NLT (b) (4) at 20 hours.
An IVIVC A has been established, which is the subject of a biopharmaceutical review.

During the CMC review this reviewer initiated several telephone calls and e-mails to the biopharm reviewer impressing upon him a potential adverse impact on the sponsor's tablet formulation program if the dissolution methodology or dissolution acceptance criteria were found to be unacceptable. To date the biopharm review is not complete nor any recommendations put forth.

SEROQUEL SR 50, 200, 300 and 400 mg tablets, have been studied for stability under ICH conditions. The stability batches had the following ratios of (b) (4) There is lack of stability information with product manufactured using other extremes (b) (4) The appearance, assay, degradation products and microbiological quality have remained within specification for the duration of the studies. Only the 50 mg strength showed any formation of degradation products, but all results remained within specifications. Minor variability is seen in the dissolution results; however, all results have met the acceptance criteria at the latest reported stability interval.
Stability studies for the 200 mg and 300 mg tablets support a shelf life of 36 months in all commercial packages when stored at 25°C.
Twelve months stability data for the 50 mg and 400 mg tablets support a shelf life of (b) (4) months (ref. 2X-ICH Q1E) in all commercial packages when stored at 25°C.

Drug Substance
The drug substance for the sustained release formulation remains unchanged compared to that (quetiapine fumurate) approved for NDA 20-639 for SEROQUEL immediate release tablets.

B. Description of How the Drug Product is Intended to be Used

SEROQUEL SR is a psychotropic agent indicated for the treatment of schizophrenia. It is to be administered once daily, preferably in the evening. The effective dose range is 400-800 mg per day depending on the response and tolerance of the individual patient. Patients who are currently being treated with devided doses of SEROQUEL (immediate release formulation) may be switched to SEROQUEL SR at the equivalent daily dose taken once daily. Individual dose adjustments may be necessary. The tablets should be swallowed whole and not split, or chewed or crushed.

C. Basis for Approvability or Not-Approval Recommendation

Approvability will be based on the sponsor's response to additional FDA review comments submitted through an IR letter dated 30-MAR-2007. These comments are the following:

1. Multivariate Model – ANN

a. Describe how changes to the ANN model (e.g., changing excipient ratios, addition/ removal/changing input variables, model modification due to numerous batch failures, new ANN model/software) would be reported to the Agency. Delineate your plan to manufacture product in the event the model is unavailable.

b. Since you have seen higher instances of dissolution prediction and actual results disagreements for the 50 mg tablets, describe your plans to refine the ANN model for the 50 mg tablet strength. Describe any (b) (4) specification restrictions that limit the material properties to those used for the training data set.

c. (b) (4)

d. Justify excluding the 1, 2, 4, 16, and 20 hour dissolution time points from model verification activities. Provide model verification results for the 1, 2, 4, 16, and 20 hour dissolution time points, if available.

e. Define the frequency of ANN model periodic reviews described in the quality management plan (see IR response to Question 3d dated January 29, 2007).

f. Define how do you plan to accommodate the impact of personnel turnover and personnel training on the ANN model.

g. Define how changes to analytical methods that support the ANN model, such as the (b) (4) content NMR method and dissolution method, impact the predictive capabilities of the ANN model.

h. Describe your plans to incorporate knowledge learned from stability results in the ANN model.

i. Detail the sensitivity of the ANN model to dissolution testing sample number. Describe how the ANN model differentiates the stage of dissolution testing (S_1, S2 or S_3).

2. Describe how the drug product stability data generated for the 50, 200, 300, 400 mg primary NDA stability batches is predictive of product stability for the other ratios (b) (4) over your proposed expiry.

3. REF: AstraZeneca Response to FDA's 'magnesium stearate' question, dated 25 January 2007 – your new data is based on tablets manufactured using a (b) (4) However, our original question remains unanswered, viz. provide information that shows how simultaneous changes, within the proposed limits, in the levels of (b) (4) and magnesium stearate concentrations would affect drug release and other parameters.

4. (b) (4)

5. Clarify the inconsistency between your statement, 'the test for Degradation products by HPLC will not be applied at the time of manufacture in P.5.6-Justification of Specification for Drug Product' and the 'Specification for Drug Product' table (P.5.1) wherein one of the test procedures is 'Degradation products by HPLC'.
We recommend that this test should be performed at release for all batches, not only the annual stability batch.

6. Provide justification for proposing 36 month shelf life based on 12 months stability data for 50 mg and 400 mg strengths – ref. P.8.1 Stability Summary and Conclusions for Drug Product.

7. The established name does not match the labeled strength. Revise all labeling using either of the following example formats:

a) SEROQUEL XR
quetiapine fumarate
Extended Release Tablets
58 mg

b) SEROQUEL XR
quetiapine
Extended Release Tablets
50 mg*

*Each tablet contains 58 mg of quetiapine fumarate equivalent to 50 mg quetiapine.
(Item 7 submitted to the sponsor through the clinical PM – Kimberly Updegraff).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Wendy Wilson
ChemistryTeamLeaderName/Date Ramesh Sood
ProjectManagerName/Date Kimberly Updegraff

C. CC Block

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/s/

Prafull Shiromani
4/24/2007 02:47:44 PM
CHEMIST

Wendy I. Wilson
4/25/2007 11:50:33 AM
CHEMIST

Ramesh Sood
4/25/2007 03:36:04 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**22-047**
Applicant:	AstraZeneca
Letter Date:	17-JUL-06
Stamp Date:	17-JUL-06
PDUFA Date:	17-MAY-07
Trademark:	Seroquel® SR
Established Name:	Quetiapine Fumarate
Dosage Form:	Extended release tablets (50, 200, 300, 400 mg)
Route of Administration:	Oral
Indication:	Schizophrenia
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary

Seroquel® was approved for the treatment of schizophrenia on September 26, 1997. Seroquel® SR Tablets have been developed to provide a once daily dosing regimen, which is expected to improve patient compliance. The sponsor had an EOP2 meeting and a Pre-NDA meeting with the Division of Neuropharmacological Drug Products. The EOP2 meeting (13-MAY-05) did not cover any CMC issues. The Pre-NDA meeting (26-OCT-05) focused on the IVIVC, formulation approach, and drug product stability protocol. Minutes for both meetings can be found in DFS.

Drug Substance

The sponsor references NDA 20-639 [Seroquel immediate release (IR) tablets; AP September 26, 1997] for information on the drug substance. Quetiapine fumarate is a white crystalline powder. It possesses no chiral centers. Quetiapine fumarate exhibits a pH dependent solubility profile over a pH range of 1 to 7.5, with maximal solubility observed at acidic pH (>80 mg/mL, pH 1.0) and minimal solubility (0.4 mg/mL) at pH 7.5. (b) (4) Quetiapine fumarate as a free base was found to be highly permeable according to the BCS guidance.

Drug Product

Seroquel® SR Tablets will be available in four extended release dosage strengths: 50 mg, 200 mg, 300 mg, and 400 mg. The recommended dose is 400 to 800 mg taken once daily, preferably in the evening. Seroquel® SR Tablets are formulated as (b) (4)

(b) (4) The model may be further simplified and/or refined as commercial manufacturing experience is obtained. The manufacture of Seroquel® SR consists of a series of consecutive processing steps that include: (b) (4) The drug product will be packaged in HDPE bottles (b) (4) and in blisters (b) (4) aluminum push-through]. The sponsor lists AstraZeneca Pharmaceuticals LP (Newark, DE) and AstraZeneca UK Limited (Macclesfield, UK) as the manufacturers of Seroquel® (quetiapine fumarate) SR Tablets.

Critical Issues for Review

- The compatibility of the excipients in the drug product should be evaluated.

- A multivariate model developed to determine the ratio of (b) (4) will need to be evaluated. The impact of the following (b) (4) factors should be included:
  - (b) (4)
  - Inter relationship between (b) (4)
  - Substitution placement on the (b) (4)
  - Effect of Morphology
  - Effect of Particle size
  - Any Function of supplier

- The adequacy of the proposed design space will need to be evaluated (e.g., in terms of experiments performed {including DOE} and data submitted). The sponsor will need to demonstrate an understanding of the release rate as function of formulation.

- The approach the sponsor plans to utilize to generate future batches should be clearly delineated, as each batch could have a unique formulation.

- The role of particle size on product performance will need to be evaluated, and if needed, adequate controls need to be in place to ensure consistent product performance. The sponsor will need to demonstrate that particle size has no clinical ramifications or that particle size (e.g., shape under the curve) as measured in clinical, stability and commercial batches is rationally controlled to ensure product performance (as outlined in labeling).

- The sponsor lists both the AstraZeneca Newark, DE and the AstraZeneca Macclesfield, UK sites as commercial drug product manufacturers. The sponsor provided stability data for debossed tablets (commercial) from the UK site and non debossed tablets from the Newark site. Commercial product test results will needed to support each site. Any differences in drug product test results by site should be determined and evaluated.

- (b) (4) blister pack films should be evaluated for the adequacy of storage

protection. The sponsor should clearly delineate which blister pack film will be marketed.

• At the pre-NDA meeting, the sponsor was informed to submit sufficient information (e.g., stress studies: evaluating for appearance/ cracking and release rate) to support the debossed tablets. In addition, the sponsor was asked to include a discussion of tooling differences between the Newark and Macclesfield sites.

• Ultimately, how any future changes (e.g., to the model) will need to be reported in terms of submission type to the agency (i.e., supplement (PA, CBE), annual report) will need to be determined. No Regulatory Agreement was submitted.

• The sponsor utilizes the sustained release designation; however, this designation does not appear in the CDER Data Standards Manual for Dosage Form.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. An **EA** has been submitted and will need to be consulted to the EA group in OPS (by the ONDQA PM). The sponsor was requested (02-AUG-06) to submit the drug substance manufacturing, packaging, and testing sites. Once these sites are submitted to the NDA, I will submit all sites into EES. The review will essentially focus on the drug product, as the drug substance has been reviewed and found acceptable in NDA 20-639. The sponsor plans on submitting a comprehensive QOS at the end of August 2006. My recommendation would be for there to be two reviewers assigned to the NDA (the review team: should have sufficient experience (i.e., senior reviewer) and also have some expertise in formulation design or DOE study design).

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/s/

Thomas Oliver
8/4/2006 12:07:42 PM
CHEMIST

Ramesh Sood
8/4/2006 12:15:38 PM
CHEMIST